Clinical Pharmacology

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Disease Progress + Drug Action

Models

- **Pharmacokinetic (dose, concentration, time)**
  - drug disposition in individuals & populations
  - disease state effects (renal & hepatic dysfunction)
  - intervention effects (hemodialysis)
  - concurrent medication effects
  - pharmacogenetic influences
- **Pharmacodynamic (dose or concentration, effect)**
  - physiologic & biomarkers
  - surrogate endpoints
  - clinical effects and endpoints

Disease Progression Model

- **Quantitative model that accounts for the time course of disease, *S(t)*, - untreated and treated** - as assessed by
  - **"Symptoms" -** measures of how a patient feels or functions ***("clinical endpoints")***
  - **"Signs" -** physiological or biological measurements of disease activity ***("biomarkers")***
    - May be linked to ***"Surrogate Endpoints"*** (biomarkers that achieve surrogacy status) or ***"Outcomes"*** (omnibus measures of global disease states such as pre-defined progression or death)

Motivations for Disease Progression Models

- Visualization of the time course of disease in treated and untreated conditions
- Evaluation of various disease interventions
- Simulation of possible future courses of disease
- Simulation of clinical trials

Model Building Process

- Talk to a Disease Specialist
- Draw pictures of time course of disease
- Translate into disease progress model
- Explain the models/parameters
- Ask Disease Specialist for advice on factors influencing parameters
- Translate into models of parameters

adapted from Holford 1999

Components of a Disease Progression Model

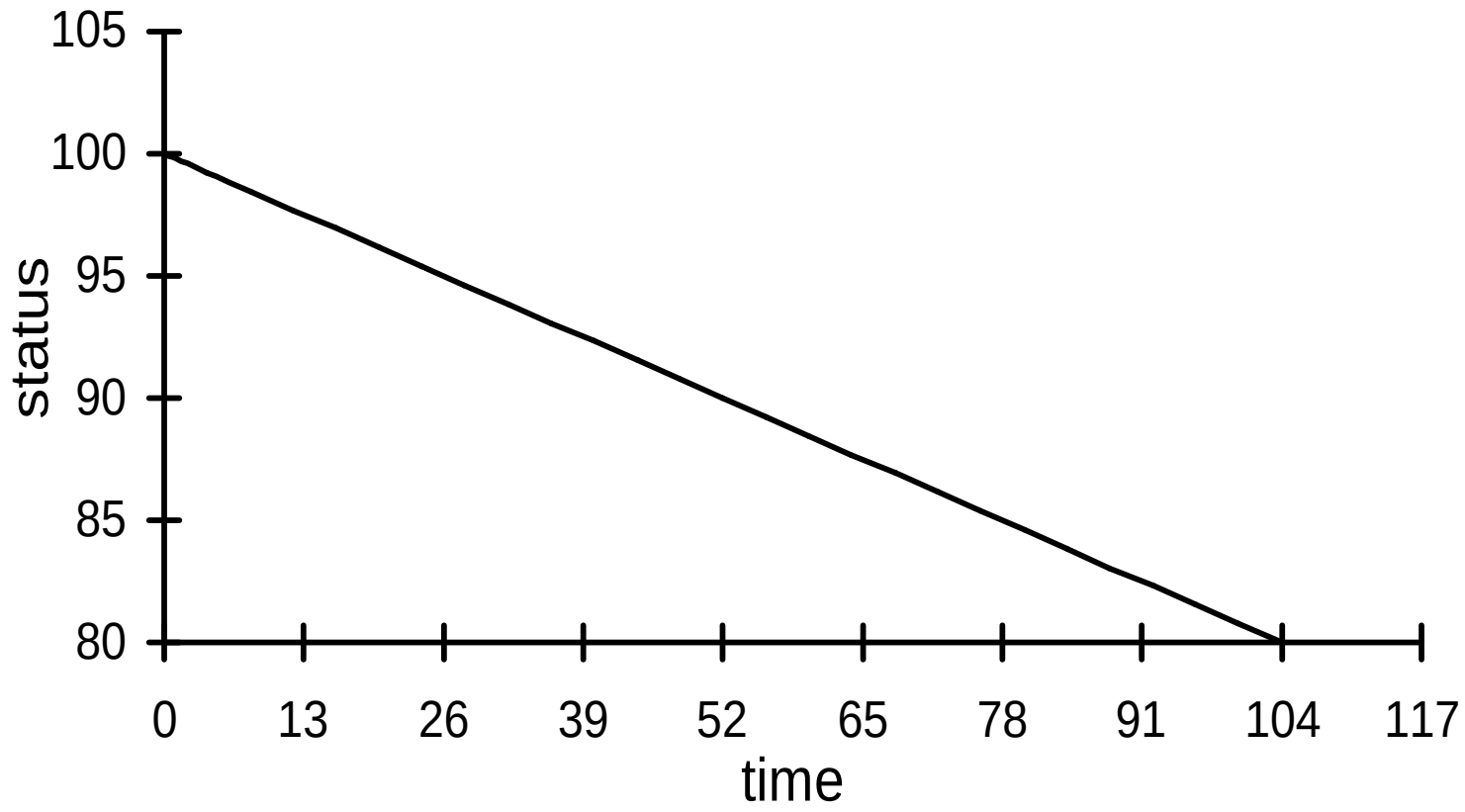
- Baseline Disease State, S_o
- Natural History
- Placebo Response
- Active Treatment Response

$$S(t) = Nat.\ Hx. + Plac + Active$$

Linear (Natural History) Disease Progression Model

(adapted from Holford 1999)

$$S(t) = S_0 + a \cdot t$$



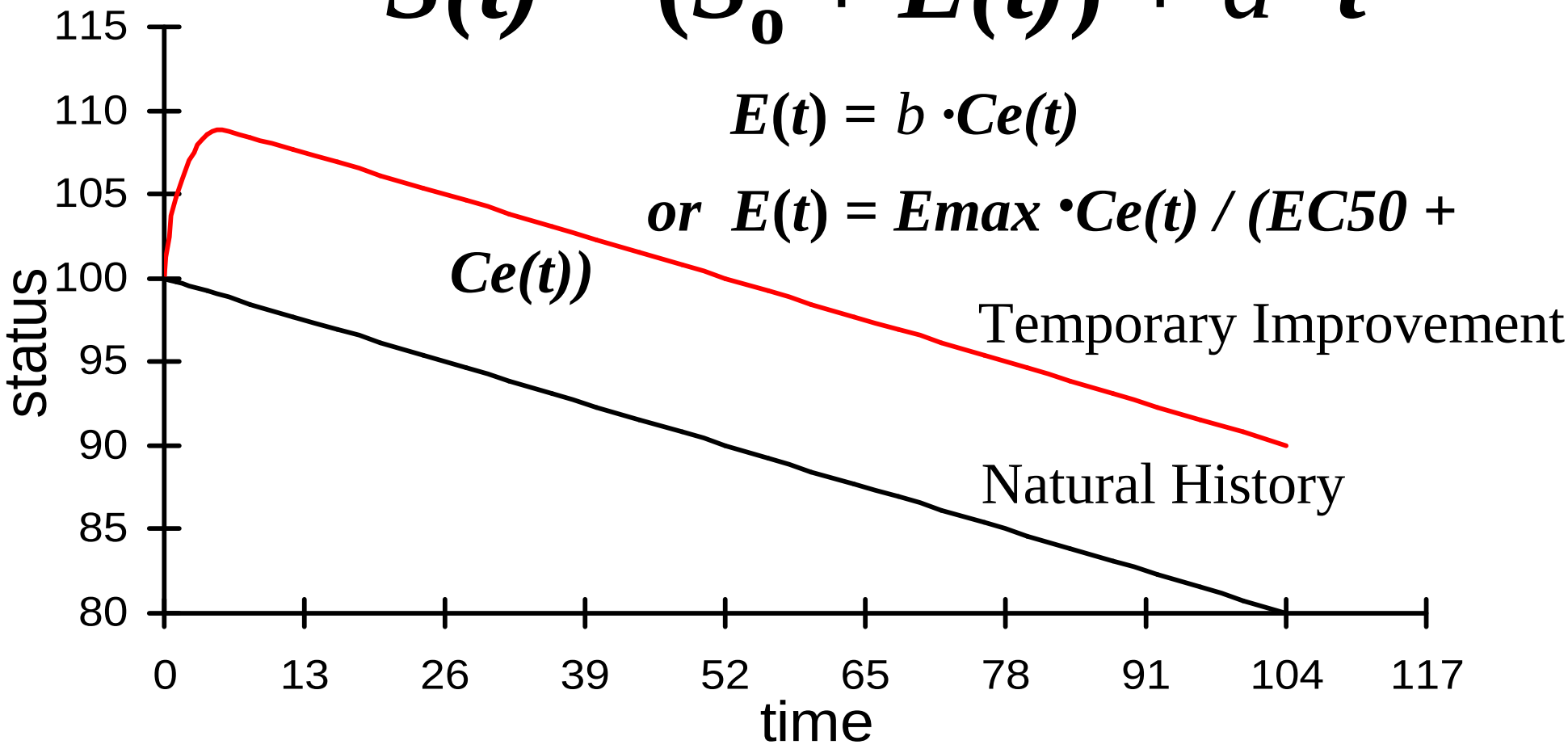
Linear Disease Progression Model with Temporary ("Offset") Placebo or Active Drug Effect

(adapted from Holford 1997 & 1999)

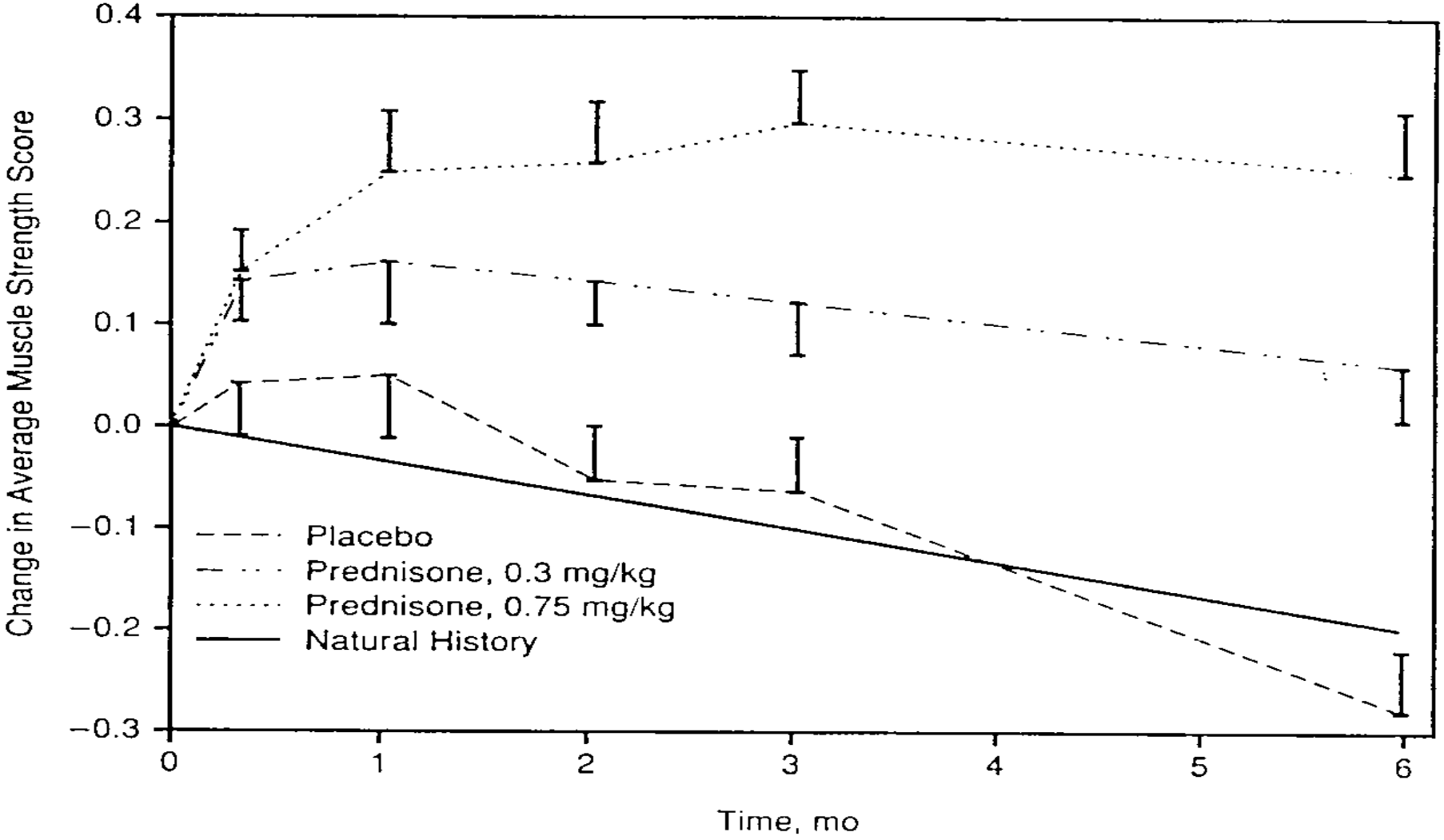
$$S(t) = (S_0 + E(t)) + a \cdot t$$

$$E(t) = b \cdot Ce(t)$$

$$\text{or } E(t) = Emax \cdot Ce(t) / (EC50 + Ce(t))$$

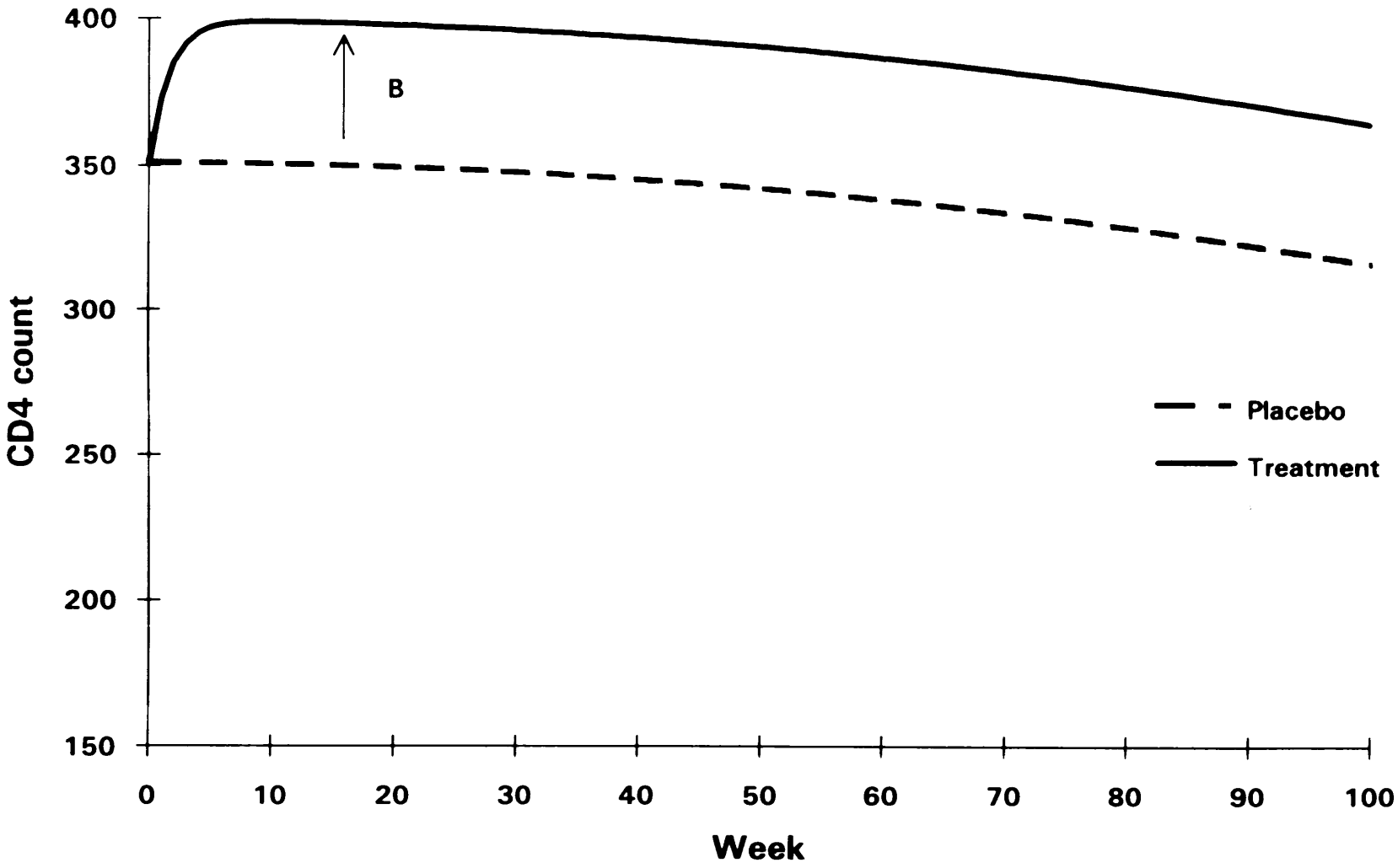


Prednisone Treatment of Muscular Dystrophy



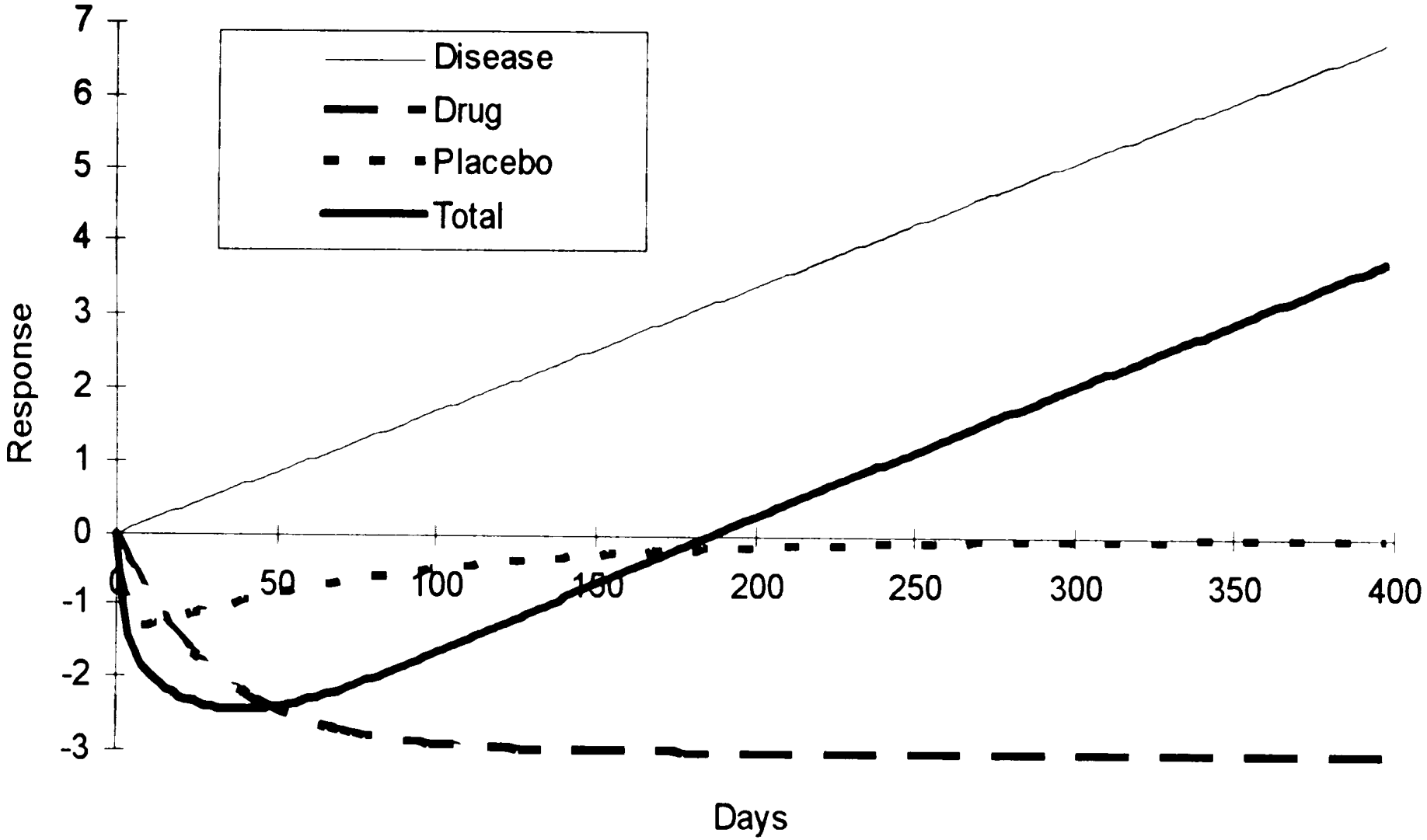
Griggs et al. Arch Neurol (1991); 48: 383-388

AZT Treatment of HIV



Sale et al, Clin Pharm Ther (1993) 54:556-566

Tacrine Treatment of Alzheimers Disease



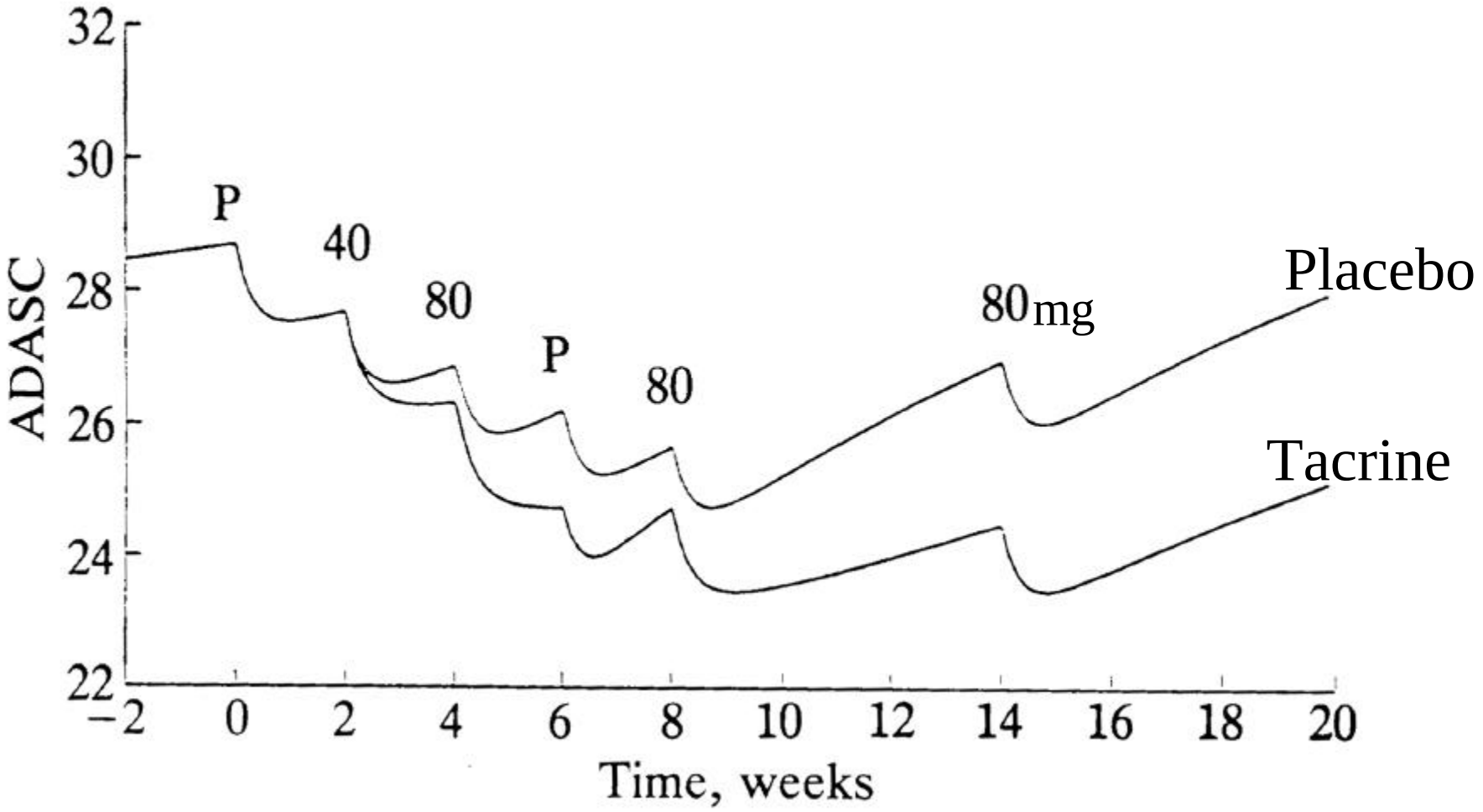
Holford & Peace, Proc Natl Acad Sci 89 (1992):11466-11470

Tacrine Treatment of Alzheimers Disease

- Baseline Disease State: S_o
- Natural History: $S_o + a \cdot t$
- Placebo Response: $b_p \cdot Ce_p(t)$
- Active Treatment Response: $b_a \cdot Ce_a(t)$

Holford & Peace, Proc Natl Acad Sci 89 (1992):11466-11470

Tacrine Treatment of Alzheimers Disease

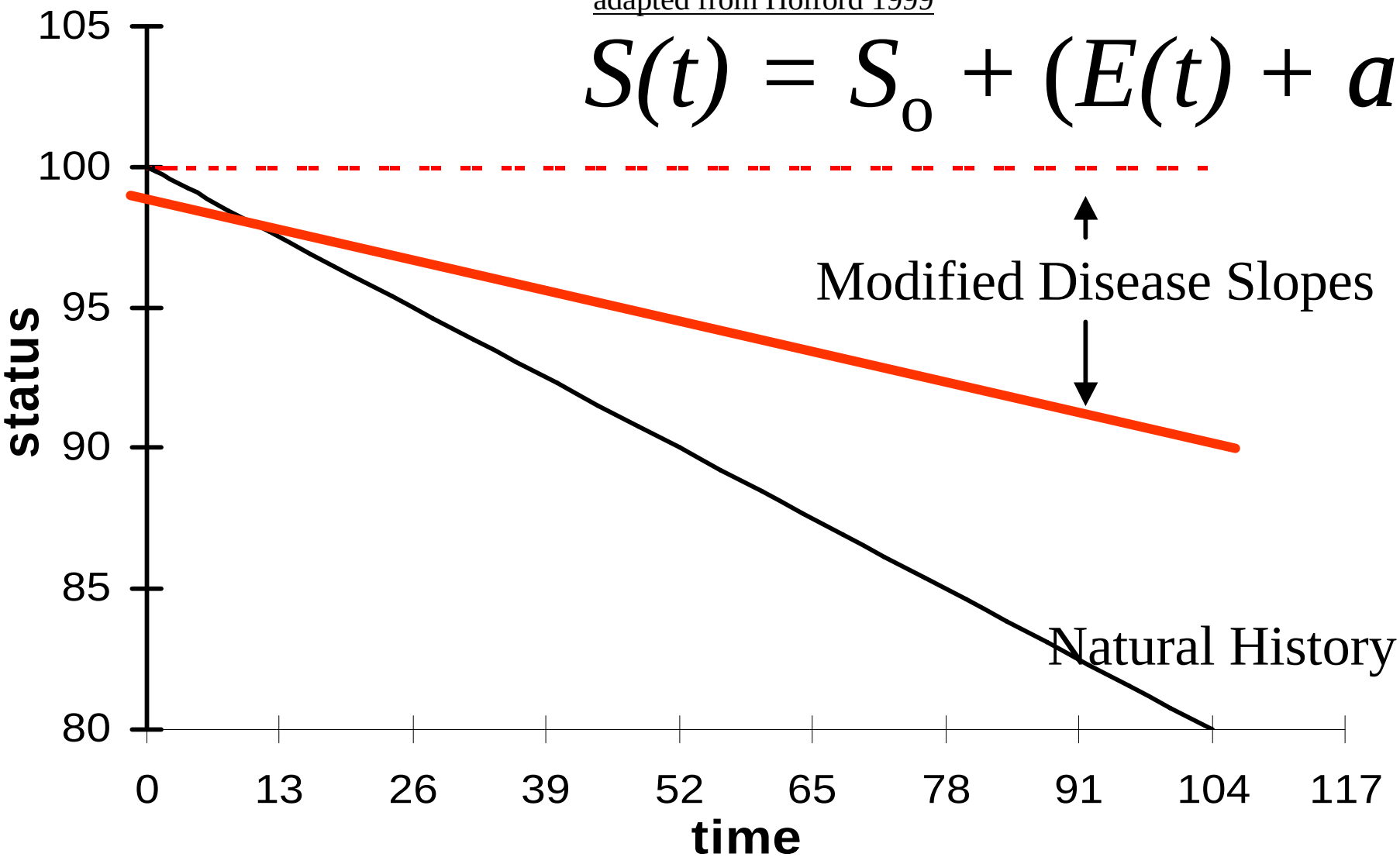


Holford & Peace, Proc Natl Acad Sci 89 (1992):11466-11470

Linear Disease Progression Model with Disease Modifying ("Slope") Active Drug Effect

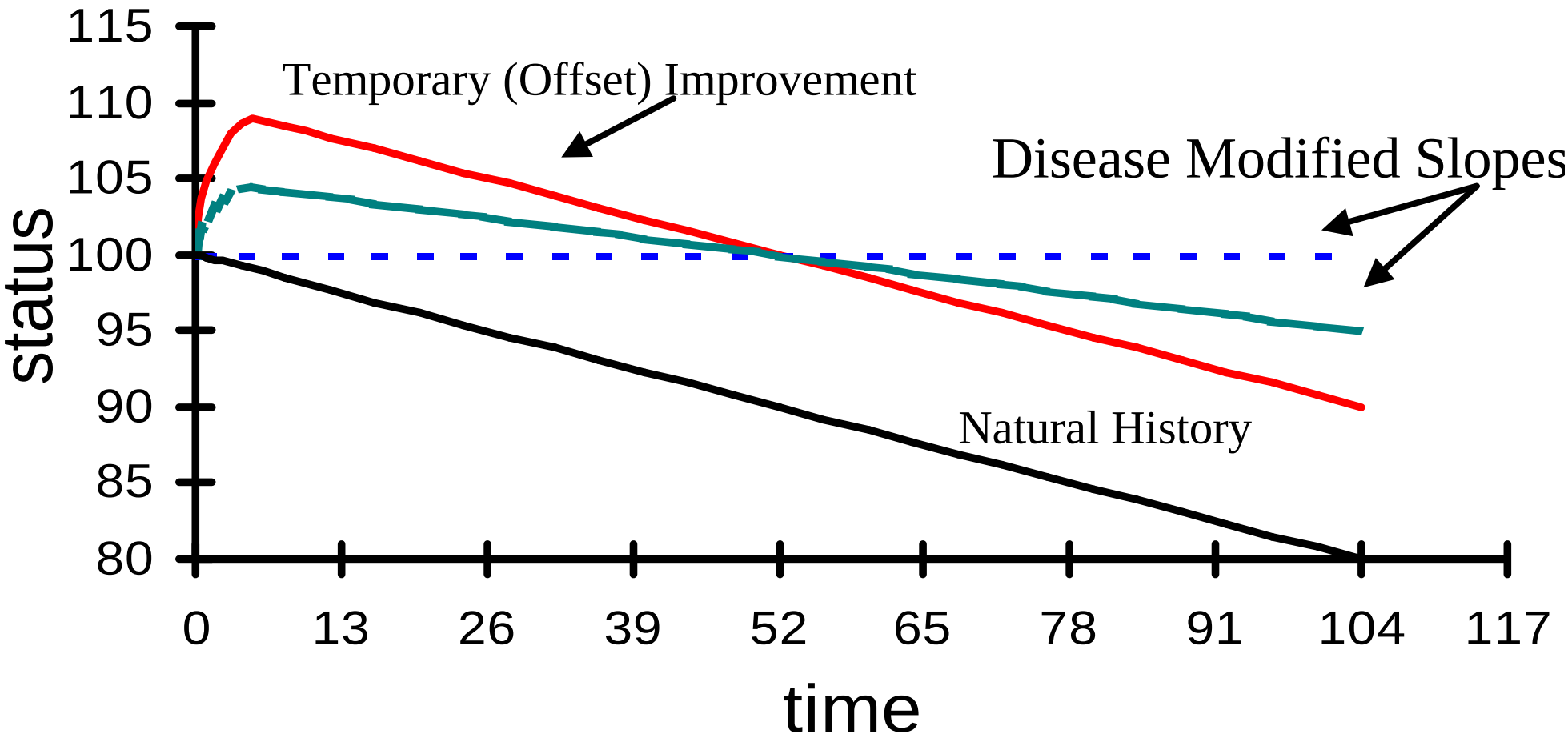
adapted from Holford 1999

$$S(t) = S_o + (E(t) + a) \cdot t$$



Alternative Drug Effect Mechanisms Superimposed on a Linear Natural History Disease Progression Model

adapted from Holford 1999



Asymptotic Progress Model

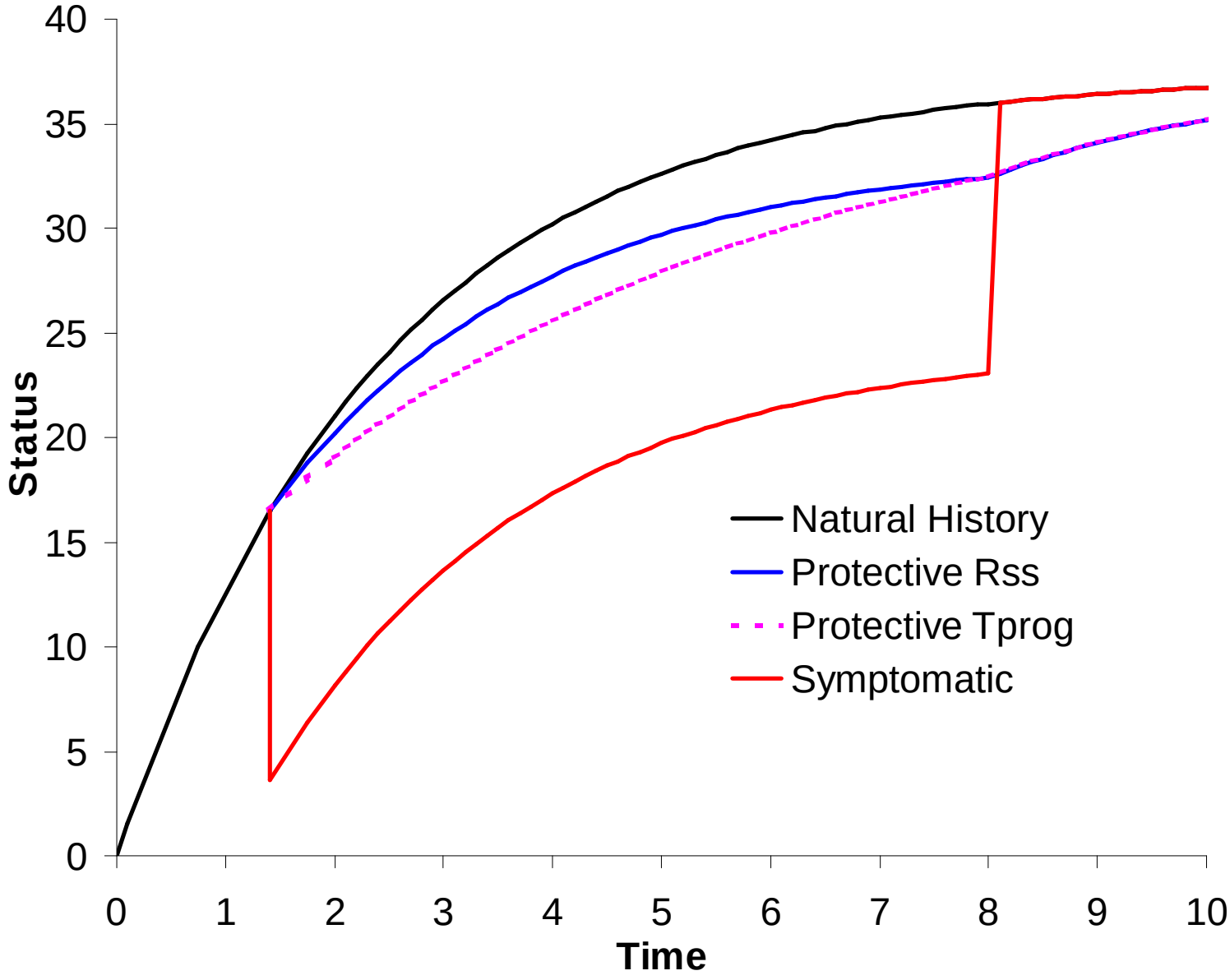
- Zero Asymptote (R_0, Tprog)
  - Spontaneous recovery

$$S(t) = R_0 \bullet e^{-\ln(2)/Tprog \bullet t}$$

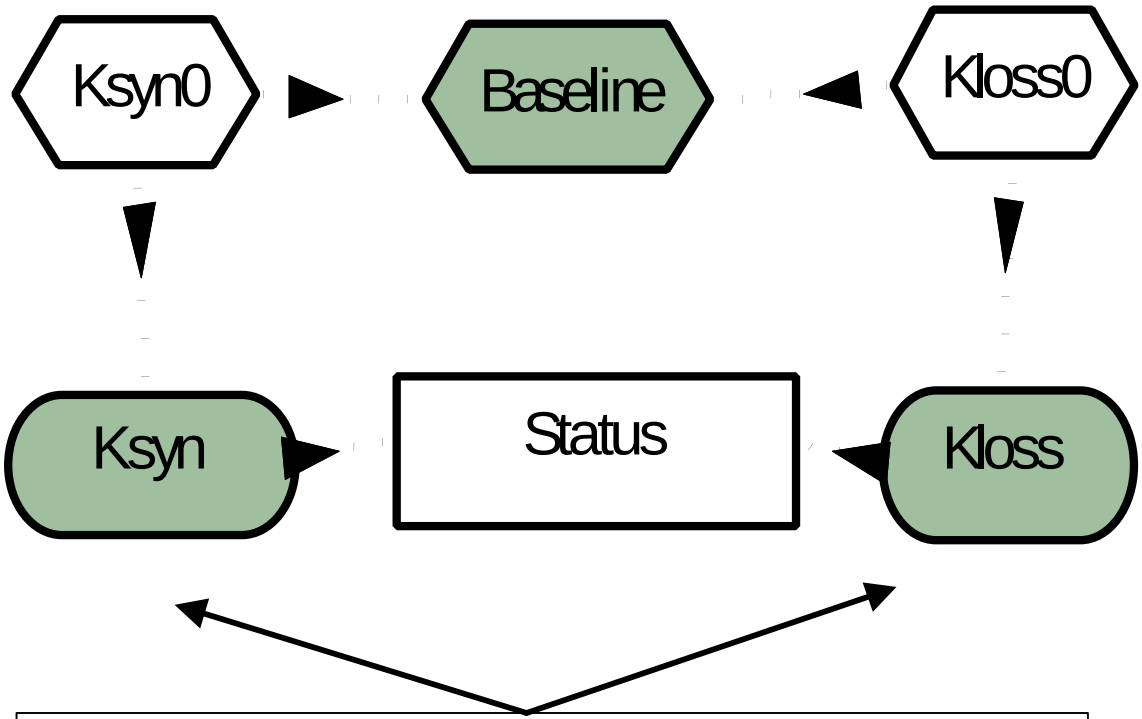
- Non-Zero Asymptote (Rss, Tprog)
  - Progression to “burnt out” state

$$S(t) = Rss \bullet \left(1 - e^{-\ln(2)/Tprog \bullet t}\right)$$

Asymptotic Progress Model

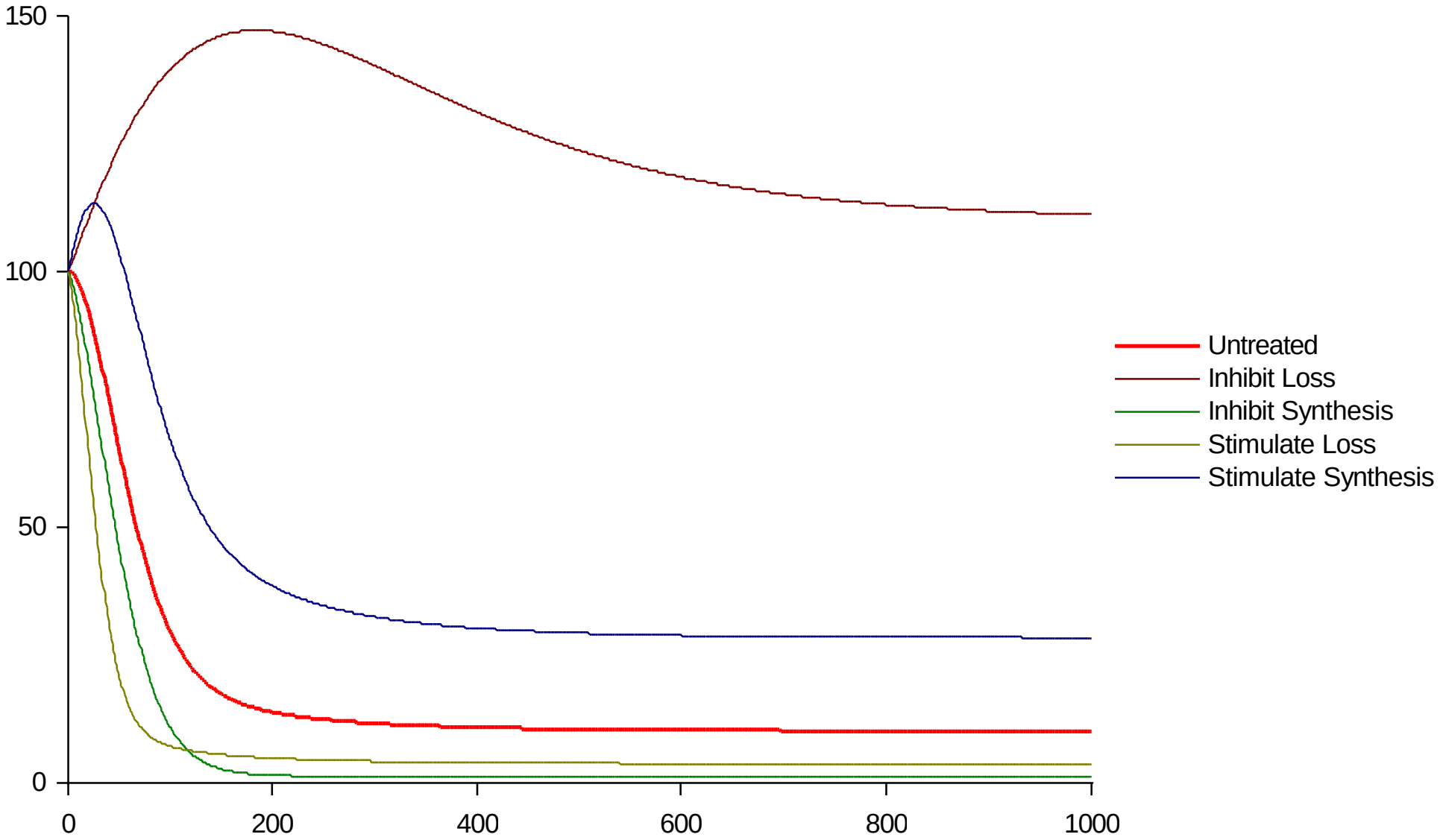


Physiological
Disease Progress

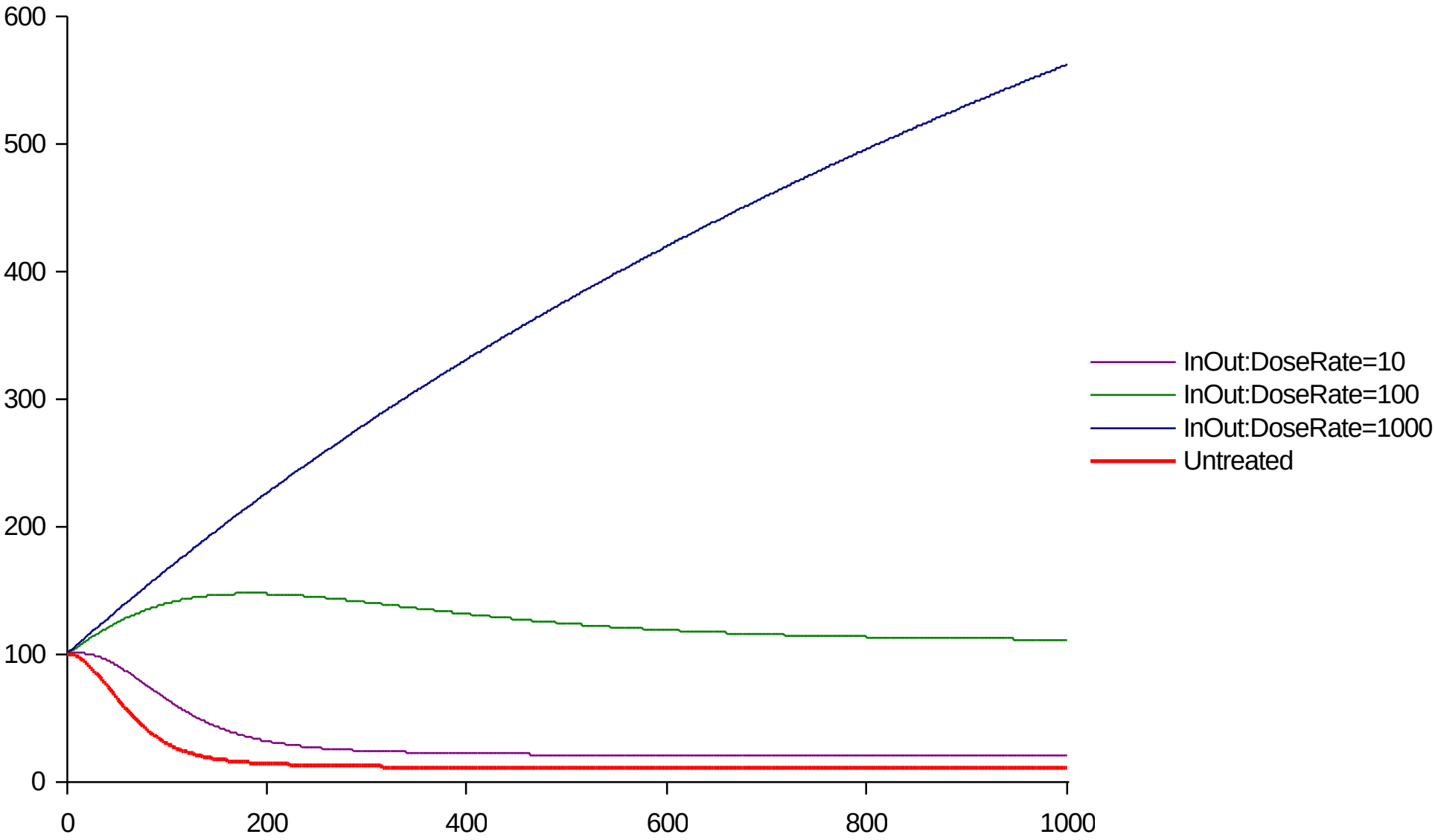


Either of these can change with time to produce disease progression

4 Basic Mechanisms



Inhibition of Loss



Disease Progress Models

- Alzheimer's Disease
  - Linear: Drug effect symptomatic
- Diabetic Neuropathy
  - Linear: Drug effect both?
- Osteoporosis
  - Inhibition of Bone Loss (oestrogen)
- Parkinson's Disease
  - Asymptotic: Drug effect both?